DRAFT CONCEPT PAPER
FOR TARGET ANIMAL SAFETY,
BIOLOGICALS
(November 16, 2000)

PROBLEM STATEMENT

Target animal safety tests are commonly required for biological products, several in the EU, Japan and the USA. They can be classified into three types.

1. General safety studies.
These are to be conducted during product development. They are intended to demonstrate the safety of administration for the target animals.

2. Specific safety studies.

These are to be conducted during product development. They are intended to identify specific characteristics of the vaccine strains such as absence of reversion to virulence, dissemination of the vaccine virus in the body and extent of shedding.

3. Batch safety tests.

These tests have to be conducted on the finished product prior to its sale to confirm the quality of each batch of product.

However, each region requires its own study/test protocols, and differences exist also in the details of the test procedure. The specifications for the animals to be used differ, as is the case for the dosages. In addition, the requirements for GLP standards differ as well. One region requires GLP standards and the others do not. These differences make the target animal safety data package generated according to the requirements of one region unacceptable or less acceptable in other regions. Presently, industry trying to register a veterinary biological product globally has to take into account all these varying requirements.

BACKGROUND

European Union.

In the EU the general safety tests (Directive 92/18/EEC, Part 7) have to be done in each target species of the most sensitive category for which the product is to be recommended. They are carried out using a single dose, an overdose (double dose for killed vaccines, and 10-fold maximum permitted dose for live vaccines) and a repeated single dose (one dose in addition to the primary vaccination program), administered by each recommended route of administration. Necropsy and histopathology may be needed for instance in case of local reactions or adjuvant residues.

Tests to demonstrate the absence of adverse effects on reproduction performance and immunological function are also required.

For live vaccines, additional tests are specified to demonstrate absence of reversion to virulence, the dissemination of the vaccine virus in the body and the extent of shedding.

The batch safety test in a target species is required for all batches of vaccine before release [Directive 92/18/EEC, Part 6E.5], using a 10 fold dose for live and a double dose for inactivated vaccines. The specification of the animals to be used for these tests, as given in the Directive, Pharmacopoeial monographs and Guidelines differ but include age, susceptibility and immune status.

Japan.

In Japan the general tests have to be done in each target species of the most sensitive category using a single dose, an overdose (maximum 10-fold dose for killed vaccines, and maximum 100-fold dose for live vaccines) and a repeated single dose given with a two-month interval. A minimum of three mammals, or ten birds or twenty fish has to be used. Necropsy and histopathology examinations, hematology and, if necessary, blood chemical examination are required.

For vaccines to be used for pregnant animals, offspring are observed for adverse effects.

The presence and depletion of adjuvant residues needs to be examined visually (MAFF guideline of safety tests).

For live vaccines, the tests to demonstrate absence of reversion to virulence, vaccine virus dissemination and shedding are required. However these tests are not categorized as part of the safety study and GLP standard is not explicitly required.
A batch safety test using the target species is required except for killed vaccine for large animals. A single dose is sufficient for most killed vaccines but overdoses are required for live vaccines.

USA.

In the USA the general tests to determine, target animal safety tests are often conducted in the field during product development.

Specific test to demonstrate absence of reversion to virulence of live vaccines are published (Memorandum No. 8000.201).

For inactivated bacterial or viral vaccines for mammalian use batch safety tests are not required in the target species, but with the final product in mice and/or guinea pigs, unless the vaccine is recommended for poultry or in case of inactivated bacterial vaccines also for fish or reptiles. For inactivated bacterial vaccines for poultry the potency test in the target bird will also serve as a safety test. When the vaccine is intended for fish or reptiles, safety tests are done in the target species in accordance with the specific standard requirements or the outline of production.
For live bacterial vaccines each lot of Master Seed shall be tested for safety in mice (9CFR113, 64(b)) unless the agent is inherently lethal for mice or if the vaccine is recommended for poultry. Each batch of live bacterial vaccine must be tested for safety in mice and in one of the species for which the product is recommended (9CFR113.64(b)(2)) in general using a double dose. Target species potency tests are used to observe adverse reactions.
For live viral vaccines, target species safety tests are required for the master seed and for each batch before release (9CFR113.300(b)). (Where the potency test is conducted in the target species, this test may also serve as target species safety test.)

The specifications of the animals used for these tests range from none to susceptible and minimum age. Specific requirements for demonstrating freedom from reversion to virulence of live vaccines are published (Memorandum No. 8000.201). For both master seed and final product also a mouse safety test is done, unless the agent is inherently lethal for mice or if the vaccine is recommended for poultry. Final product safety tests in target animals shall be done with a 10-fold dose.

PROPOSAL FOR RESOLUTION

The VICH Working Group on Target Animal Safety should develop a harmonized guideline for target animal safety studies, both for general and specific safety studies as required for biological products including genetically modified organisms. These studies should constitute the minimum requirements for safety.

The Working Group shall establish a generalized guideline applicable to all animal species, but shall distinguish between the requirements for live and killed vaccines. The working group will not develop a specific guideline for minor species.

The Working Group will also discuss whether the group should establish a generalized guideline for batch release testing, although the primary function of the Working Group is to develop harmonized guidelines required for registration of biological products.

The Working Group will develop a separate alone standing harmonized guideline for specific veterinary biological products.

IMPACT

A harmonized guideline will enable industry to design target animal safety studies that will be accepted in all three regions. This will minimize animal testing, reduce the number of experimental animals and avoid duplication of studies.

PROPOSED TIME FRAME

1st stage - The first meeting in November 2000 will prepare the draft step 2 document for pharmaceutical products and review the concept paper for biological products.

2nd stage - 1 or 2 meetings, 1 year to finalize Step 2 recommendations for pharmaceutical products and prepare draft step 2 document for biological products.

3rd stage - 1 or 2 meetings 1 year to finalize Step 2 recommendations for biological products.

Comparative Requirements for Biologicals in Japan, the EU and the USA

Topic	Japan	EU	USA
General safety test			
Animals	- Target species - History of feeding and medication, management details prior to study identified - Most sensitive age - Immunological status identified - Non-pregnant and pregnant (if indicated)	-Target species -Healthy -Most sensitive -Pregnant (if indicated)	- Target species in cause of live viral vaccines - Mouse (live vaccines)
Number of animals	- Mammals: 3 or more animals - Chickens: 10 or more birds - Aquatic species:>20 or more fish	-An adequate number of animals or units per group.	- Dog + cat:10 - Calf, sheep, pig:2 - Chicken:25
Route of administration	- Most likely route to reveal adverse effects - In case of vaccines containing adjuvant, all recommended administration routes	-Each recommended route on the label	- Target animal: Recommended route on the label - Mouse: intracerebral/interperatonea
Doses	- Minimum of two treated groups and an untreated control group - Included a dose at which adverse effects are observed (maximum 10 doses for killed and 100 doses for live) and a no adverse effect dose (one dose).	-Recommended dose (formulated at maximum titer/potency) and overdose (2 doses for killed and 10 doses for live) -Repeated administration of one dose may be required	- Varies from 1 to 10 doses - Mouse: 0.03ml/0.5ml
Duration of administration	- Recommended administrations with programmed interval - Additional one more dose after 2 months from last administration (if vaccine used more than 2 times in life)	-Recommended administration.	- Recommended administration.
Observations			
- General	- Daily clinical observation - Necropsy and histopathology examinations - Hematology and, if necessary, blood chemical examination	-Macroscopic and microscopic examinations of local and systemic reaction -Rectal temperature and performance -Injection site histopathology, if necessary	- Observation of any adverse effect.
- Pregnant animal	- Clinical observation for pregnant animals and offspring - Reproductive performance	-Reproductive performance, if a potential risk factor considered	
- Adjuvant residue	- Examination of residue depletion		
- Immunological function	- If adverse effect considered	-If adverse effect considered	
Test standards	- GLP	-GLP	

Specific tests required for live vaccines Reversion to virulence	- At least 5 serial passages or until organism shedding disappears from the target animal - Intermediate in vitro passage not allowed	- At least 5 serial passages through target animal or until organism shedding disappears. Then confirmation test to be done. - Intermediate in vitro passage allowed.	- Total of 5 serial passages through target animal - Intermediate in vitro passage not allowed
Dissemination	- Dissemination to organs and excretion	- Dissemination to organs, tissues, faeces, urine, milk, egg, oral, nasal and other secretions	- May be combined with reversion study
Spread of vaccine strain	- Spread from vaccinated to unvaccinated target animals	- Spread from vaccinated to unvaccinated target animals, if necessary, to non-target species also	
Test standards	- Proof of test reliability required	- GLP	
Batch release test Generals	- May be combined with target animal potency test		- In mice or guinea pig when potency test is in a target species
Requirements - Number of animal - Animal status - Dose	- Varies with product - Varies with product - Single dose, 10 doses for avian live vaccines	- Mammals 2, birds 10 - Varies with product - 2 doses for killed, 10 doses for live	- Mammals 2, poultry 25 - Varies with product - 2 doses for killed and for live bacterial vaccine, 10 doses for live viral vaccine when done in target animal
- Observation period	- Varies with product (2 to 7 weeks)	- 14 days	- 14 days for dog and cat, 21 days for calf, swine and sheep
- Observation	- General sign	- Local and systemic reaction	- unfavorable reactions
Test standards		- GLP	